REMARKS

The undersigned thanks the Examiner and her supervisor for the very helpful and

productive interview, in regard to the instant application, held on March 21, 2003.

Claims 1, 3-23, 26-40 and 42-50 are all the claims pending in the application. Claims

14 and 31-39 have been withdrawn from consideration. Claims 1, 3-13, 15-23, 26-30, 40 and

42-50 are rejected.

In view of the restriction requirement, claims 14 and 31-39 are being canceled herein,

without prejudice or disclaimer.

After entry of the amendment, claims 1, 3-13, 15-23, 26-30, 40 and 42-50 will be

pending.

Claim 1 has been amended to allow the variable X to be either (A-B-C-A), (A-C-B-

A), or a combination of both, in the same peptide. Detailed support for the amendment is

provided under point **II. B.** below.

Claim 1 has also been amended to more clearly state that each R^1 in R^1_a, each R^2 in

R^2_b and each R^3 in R^3_c are independently the same or different from each other.

Claim 5 has been amended to correct the antecedent basis of variables recited in the

claim.

Claims 8-12 have been amended to insert the term "isolated" into each of the claims,

thereby explicitly indicating the hand of man in the claims. Support of the amendment is

inherent in the specification as any method of producing the peptides recited in the claims

would inherently required the isolation of the peptides in some manner.

Claim 42 has been amended to correct the variables recited in the claims such that

they are in agreement with the variables used in claim 1, the claim from which claim 42

depends.

No new matter has been added. Entry of the amendment is respectfully requested.

I.   Oath/Declaration

At paragraph 1 of the Office Action, the Examiner states that the declaration is

defective because the declaration submitted with the instant application refers to entering the

national stage, while the instant application is a continuation-in-part of PCT/NL97/00449 as

indicated in the preliminary amendment.

In response, Applicants include herewith an executed Declaration and Power of

Attorney, correctly referring to the instant application as a continuation-in-part of the PCT

application. Applicants respectfully request the Examiner acknowledgment receipt of the

same, and withdrawal of the instant objection.

II.   New Matter Objection

At paragraph 4 of the Office Action, the amendment filed July 8, 2002[1] is objected to

under 35 U.S.C. §132 because it allegedly introduces new matter into the disclosure.

The Examiner states that the specification does not support a purified peptide having

the formula (I), R^1_a-R^2_b-A-B-X_m-C_n-R^3_c, where X is (A-C-B-A).

Applicants' response

A.   During the interview of March 21, 2003, the Examiner indicated that because

formula (I) recited the orientation "(A-B-C-A)$_m$" (in the claim as originally filed, but now

amended to be "X_m"), in the situation where m is 2 or greater each of the motifs would be

required to be the same, i.e., (A-B-C-A)-(A-B-C-A). Thus, while all of the motifs could be in

the forward orientation (i.e., (A-B-C-A), the scope of the claim did not include peptides

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[1]   While the Examiner refers to a supplemental amendment filed April 22, 2002, Applicants
respectfully note that no such paper was filed. Applicants therefore believe that the Examiner is
referring to the Amendment Under 37 C.F.R. §1.111 filed July 8, 2002.

where all of the motifs were in the reverse orientation, or there was a mixture of the motifs in

both orientations in the same peptide.

Applicants respectfully assert that the identity and meaning of the variables in a

formula, such as those in formula (I) of claim 1, may be defined in the body of the claim in

any manner that makes clear the identity and meaning of the variables used in the formula.

Thus, while formula (I), as originally recited in the claim, includes the motif "$(A\text{-}B\text{-}C\text{-}A)_m$",

Applicants may define the motif in the body of the claim in any manner that does not make

the formula itself, or other variables in the formula, unclear or indefinite.

Therefore, while formula (I) includes the motif "$(A\text{-}B\text{-}C\text{-}A)_m$" in the claim, a proper

claim can further define the motif as being in either the orientation shown in the formula, or

in a retro orientation (i.e., (A-C-B-A)).

That being said, Applicants also assert that there is support in the specification for

peptides of formula (I) wherein all of the motifs (A-B-C-A), now defined as X, are in either

the forward or reverse orientation.

Applicants first note that "X" in formula (I) is defined as "either (A-B-C-A) or (A-C-

B-A)" at line 18 of claim 1. Further, m is defined as "an integer of from 2 to 8." Thus,

Applicants are claiming in one embodiment of the invention, a peptide of formula (I) that

may have between 2 and 8 copies of the motif X, where each copy is in the orientation (A-C-

B-A). And in another embodiment, Applicants are claiming a peptide of formula (I) that may

have between 2 and 8 copies of the motif X, where each copy is in the retro orientation (A-B-

C-A).

Support for this embodiment of the claim may be found at page 10, lines 24-29, of the

application. Therein, it is stated that "at least 0-m of the repetitive sequence motifs ($A_2\text{-}B_2\text{-}$

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C_1-A_3) have the retro orientation and the remaining repetitive motifs (A_2-B_2-C_1-A_3) have the orientation as present in the formula." At line 29, it is stated that "m=1-10."

If m is defined as "10", then the specification is stating that at least 0-10 of the motifs have the retro orientation, and the remaining motifs have the orientation as presented (i.e., the forward orientation).

Thus, if <u>none</u> of the motifs (m=0) have the retro orientation, then <u>all</u> of the motifs (the "remaining" motifs) have the forward orientation (i.e., (A-B-C-A)). Thus, there is clear support for X = (A-B-C-A).

Similarly, if <u>all</u> of the motifs (m=10) have the retro orientation, then <u>none</u> of the motifs (the "remaining" motifs) have the forward orientation (i.e., (A-B-C-A)). Thus, there is clear support for X = (A-C-B-A).

B. Applicants also include herewith an amendment to claim 1, such that the motif X is being defined to include those peptides having at least one motif X in the forward orientation and at least one motif X in the retro orientation, in the same peptide (in addition to those peptides where all of the motifs X in the peptide are in the forward orientation, and those peptides where all of the motifs X are in the reverse orientation).

This amendment finds support in the same section of the specification discussed above, namely, page 10, lines 24-29. Again, it is stated therein that "at least 0-m of the repetitive sequence motifs (A_2-B_2-C_1-A_3) have the retro orientation and the remaining repetitive motifs (A_2-B_2-C_1-A_3) have the orientation as present in the formula."

Thus, if the total m as defined in formula (I) is 8, for example, then one embodiment of claim 1 could be where "at least 0-m [5, for example] of the repetitive sequence motifs (A_2-B_2-C_1-A_3) have the retro orientation and the remaining repetitive motifs (A_2-B_2-C_1-A_3) [3] have the orientation as present in the formula."

Another embodiment where the total m as defined in formula (I) is 8, could be where

"at least 0-m [2, for example] of the repetitive sequence motifs $(A_2-B_2-C_1-A_3)$ have the retro

orientation and the remaining repetitive motifs $(A_2-B_2-C_1-A_3)$ [6] have the orientation as

present in the formula."

Any combination of forward and retro orientations where the number of motif X is

equal to 8, and there is at least one motif X in the forward direction and one motif X in the

retro orientation would be included.

Thus, as seen from this example, there is clear support for motif X being both (A-B-

C-A) and (A-C-B-A) in the same peptide.

In view of the points discussed above, Applicants assert that no new matter has been

introduced into the application, and therefore respectfully request reconsideration and

withdrawal of the rejection.

III.   Rejection of Claims Under 35 U.S.C. §101

At paragraph 5 of the Office Action, claims 8-12 are rejected under 35 U.S.C. §101 as

being directed to non-statutory subject matter.

The Examiner states that the claims do not indicate the hand of man.

In response, Applicants note that the Examiner has not identified any prior art which

indicates the claimed peptides are naturally occurring. However, to further prosecution of the

application, Applicants include herewith an amendment to the cited claims, inserting the term

"isolated", thus explicitly indicating the hand of man. Support of the amendment is inherent

in the specification as any method of producing the peptides recited in the claims would

inherently required the isolation of the peptides in some manner.

The remainder of the claims has also been amended so that they there are consistent

with claims 8-12 in reciting "isolated" peptides.

In view of the amendments, Applicants assert the rejected claims recite statutory subject matter, and therefore respectfully request reconsideration and withdrawal of the rejection.

IV.   Rejection of Claims Under 35 U.S.C. §112, first paragraph

At paragraph 6 of the Office Action, claims 1, 3-7, 13, 15-23, 26-30, 40 and 42-50 are rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description support in the specification as filed.

The Examiner states that while the claims are directed to peptides of formula (I) where the motif X is (A-B-C-A) or (A-C-B-A), the specification does not describe peptides of formula (I) wherein all motif X are in the retro orientation (A-C-B-A), and that there is no disclosure of making and using such peptides. The Examiner explains that the examples provided in the specification are only those peptides which have both (A-B-C-A) and (A-C-B-A) motifs.

In response, Applicants assert that they have sufficiently described the claimed invention, in such full, clear, concise terms that a skilled artisan would recognize applicants were in possession of the claimed invention at the time the application was filed.

As recited in claim 1 of the application, the peptides of the present application encompass a limited group of molecules. Each member of the group has between 12 and 67 amino acids, and each member is amphipathic, cationic and forms a stable α–helix.

Furthermore, the skilled artisan reviewing formula (I) would understand that it is the central portion of the formula that is the active portion of the molecule. First, the motif defined by X is any combination of between 2 and 8 copies of the motif (A-B-C-A), where all of the motif X may be in the forward orientation, all may be in the retro orientation, or where there may be a mixture of both orientations. Close inspect reveals that no matter the make up

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of this portion of the molecule, there is a four amino acid repeat, where the first and fourth

residues are basic amino acids (BAA), and the second and third residues are neutral amino

acids (NAA). Thus, no matter the make up of the peptides encompassed within formula (I),

each will have between 2 and 8 regular repeating regions. For example, where m = 2, the

peptides will each have the following motif:

m = 2:   BAA-NAA-NAA-BAA - BAA-NAA-NAA-BAA

It is important to note that no matter the orientation of the motif (i.e., (A-B-C-A) or

(A-C-B-A), the make-up of the motifs will be the same, two neutral amino acids bounded by

two basic amino acids.

The other central portions of the formula (I) that are important for function are the

"A-B" residues on one side of the motif X, and the variable "C_n" on the other side of the

motif X. These variables specify that each peptide of the formula will have a basic amino

acid-neutral amino acid pair on one end of the motif X, and a string of between 1 and 3

hydrophobic amino acids on the other end of the motif X.

Together, this central portion of formula (I) results in peptides that are amphipathic,

cationic and that form a stable α-helix. And it is the specific physical characteristics of this

central portion of the formula that give the peptides their activity. As stated in the

specification at page 15, lines 8-10, "the absolute requirement for a tandem array of 2 or more

of the repetitive sequence motifs $(A_2-B_2-C_1-A_3)_m$ flanked by a hydrophobic C-terminal

domain $(C_2)_n$, was demonstrated with the use of the BP1.1, BP2.1 derivatives [control

sequences]."

The reminder of the formula, i.e., the amino- and carboxy-termini ($R^1_a-R^2_b$ and R^3_c),

may be comprised of any combination of amino acids, but the length is restricted such that

there can only be up to 15 amino acids at the amino-terminus, and up to 15 amino acids at the

carboxy terminus. That the identity of the residues in this portion of the molecule is not

specified demonstrates that the amino- and carboxy-termini simply help to stabilize the

peptides, but are not the active portion of the molecule. Indeed, the fact that both R^1_a-R^2_b and

R^3_c may be absent (where a, b and c all equal 0) from the peptides is further proof that it is the

central core of the formula that has the functional activity of the peptides encompassed within

formula (I).

As can be seen from this discussion, Applicants have defined in great detail a small

group of highly related peptides. Thus, Applicants have clearly and sufficiently described the

claimed invention in such full, clear, concise terms that the skilled artisan would recognize

that Applicants were in possession of the claimed invention at the time the application was

filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of this

rejection.

V.   Rejection of Claims Under 35 U.S.C. §112, second paragraph

A.   At paragraph 7 of the Office Action, claims 5, 6, 42 and 48 are rejected under

35 U.S.C. §112, second paragraph, as being indefinite.

(1)   The Examiner states that claim 5 recites the limitation "R^1-R^2" in line 1, but

that there is insufficient antecedent basis for this limitation in claim 1.

In response, Applicants include herewith an amendment to claim 5, correcting the

noted variables of the formula, such that they are fully supported, in terms of antecedent

basis, by claim 1.

(2)   The Examiner states that claim 6 recites the limitation "motifs (A-C-B-A) are

present in said peptide in a greater amount than motifs (A-B-C-A)" in lines 1-2, but that there

is insufficient antecedent basis for this limitation in claim 1.

In response, in view of the amendment to claim 1 discussed above, claim 6 now has

proper antecedent basis in claim 1 as formula (I) may contain both (A-B-C-A) and (A-C-B-

A) motifs. No amendment to the claim is required.

(3)   The Examiner states that claim 42 recites the limitation "x and y are each 0" in

line 1, but that there is insufficient antecedent basis for this limitation.

In response, Applicants include herewith an amendment to claim 42, correcting the

variables recited in the claim, such that they are in agreement with the variables used in claim 1.

(4)   The Examiner states that claim 48 recites the limitation "R^2 is ACAA" in line 1,

but that there is insufficient antecedent basis for this limitation in claim 1 because $R^2_{b=4}$ can

only be AAAA, and R^2 cannot be a peptide of ACAA.

In response, Applicants refer to their comments above in section **II. A.** As discussed

therein, the identity and meaning of the variables in a formula, such as those in formula (I) of

claim 1, may be defined in the body of the claim in any manner that makes clear the identity

and meaning of the variables used in the formula. Thus, while formula (I) includes the motif

"R^2_b", not all R^2 are required to be the same amino acid when b=4. Applicants may define

the motif in the body of the claim in any manner that does not make the formula itself, or

other variables in the formula, unclear or indefinite. As Applicants include in the body of the

claim that <u>each</u> R^2 in R^2_b may be any amino acid, and that the amino acids in R^2_b may be the

same or different, the recitation "R^2 is ACAA" in claim 42 has proper antecedent basis in

claim 1. No amendment to the claim is required.

(5)   The Examiner maintains point (i) of the previous rejection of claim 1, namely,

that the formula (I) is not reflected in the written part of claim 1 describing the formula in

claim 1. The Examiner states that while the formula (I) has been amended to indicate the

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motif may be present in either (A-B-C-A) or (A-C-B-A), peptides that only contain the motif

(A-C-B-A) are not described in the specification.

In response, Applicants again refer to their arguments above, and assert that a peptide

that only contains the motif (A-C-B-A) is described in the specification for the reasons set

forth in section **II. A.** above.

(6)   The Examiner maintains point (ii) of the previous rejection of claim 1, namely,

that the dependent claims are not consistent with formula (I) of claim 1. The Examiner states

that claims 5, 6, 42 and 48 have not been amended to be consistent with claim 1.

In response, Applicants include herewith amendments to claims 5 and 42, discussed

above, making them consistent with claim 1. With regard to claims 6 and 48, Applicants

assert that these claims are consistent with claim 1, for the reasons set forth in sections **V. A.**

(2) and **V. A. (4)**, respectively.

(7)   The Examiner maintains point (iii) of the previous rejection of claim 1,

namely, that the sequences of BP1, BP2, BP2.3, BP2.4 and BP2.5 do not conform to formula

(I) of claim 1 because peptides of formula (I) may contain only (A-B-C-A) or (A-C-B-A), but

not both, as is the case for BP1, BP2, BP2.3, BP2.4 and BP2.5.

In response, as discussed above in section **II. B.**, Applicants include herewith an

amendment to claim 1 such that it is clear that the peptides of formula (I) include those

peptides comprising both (A-B-C-A) and (A-C-B-A).

The Examiner further states that in comparison to BP1, the formula (I) is not correctly

described because R^1_2 means R^1-R^1, which can only be Gly-Gly or Arg-Arg, not Gly-Arg.

In response, Applicants note that claim 1 has been amended such that it is clear that

each R^1 in R^1_a, each R^2 in R^2_b, and each R^3 in R^3_c may be any amino acid, and may be the

same of different from the other R^1 in R^1_a, the other R^2 in R^2_b, and the other R^3 in R^3_c.

In view of the amendments to the claims, and the points discussed above, Applicants

assert that each of the rejected claims is definite as written, and therefore respectfully request

reconsideration and withdrawal of this rejection.

B.   At paragraph 8 of the Office Action, claims 1, 3-7, 13, 15-23, 26-30, 40 and

42-50 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite.

The Examiner states that the use of the phrase each "R^1, R^2 and R^3 are each an amino

acid and may be the same or different " renders the claim indefinite because it is unclear what

peptide is intended for the formula, e.g., which amino acid is being used as R^1, R^2 and R^3.

In response, Applicants include herewith amendment to claim 1 such that it is clearly

stated that each R^1 in R^1_a, each R^2 in R^2_b, and each R^3 in R^3_c may be any amino acid, and may

be the same of different from the other R^1 in R^1_a, the other R^2 in R^2_b, and the other R^3 in R^3_c.

Furthermore, for the reasons discussed above in section **II. A.**, Applicants assert that

such an amendment makes clear which amino acids are being used as R^1, R^2 and R^3. The

identity and meaning of the variables in a formula, such as those in formula (I) of claim 1,

may be defined in the body of the claim in any manner that makes clear the identity and

meaning of the variables used in the formula. Thus, while formula (I) includes the motif

"R^2_b", for example, not all R^2 are required to be the same amino acid when b=4, for example.

Applicants may define the motif in the body of the claim in any manner that does not make

the formula itself, or other variables in the formula, unclear or indefinite. As Applicants

include in the body of the claim that <u>each</u> R^2 in R^2_b may be any amino acid, and that the

amino acids in R^2_b may be the same or different, the recitation is definite. The same is true for

each R^1 in R^1_a and each R^3 in R^3_c.

As can be seen in the peptide BP2.5, R^3 is both Gly and Cys. And at page 11, lines 3-4, of the specification, it is clearly stated that R^1 may be Gly and Ala, thus it is also clear that there may be at least two different amino acids in R^1.
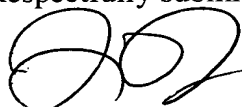
For these reasons, Applicants assert that claim 1 is definite as set forth in the amended claims herein, and therefore respectfully request reconsideration and withdrawal of the rejection.

VI.   Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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